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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,227	MAHAN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1042004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,9-18,24,28-33 and 47-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3,5-7,9-10,12-15,24,28-33,47-50* is/are rejected.

7)☐ Claim(s) *1,16-18 and 511* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1,3,5-7, 9-18,24,28-33,47-50 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Allowable Subject Matter

2. Claims 11, 16-18 are objected to as being dependent upon a rejected and objected to base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 4,2004 has been entered.

Response to Arguments

1. All prior art rejections are herein withdrawn in light of new grounds of rejection set forth below.

Claim Objections

2. Claims 1 and 5 are objected to because of the following informalities:

3. Claim 1 recites the term "tetranucelotide" is misspelled; this should be

-----tetranucleotide-------.

4. Claim 5 depends from claim 1 and defines the agent to be "a dam gene construct that expresses DNA methyltransferase" while claim 1 defines the agent to be an agent that "prevents" the bacteria's dam gene expression. Claim 5 broadens the scope of claim 1 to include bacteria that express dam DNA methyltransferase activity. There is no guidance or teaching that the bacterial dam DNA methyltransferase activity is negative regulated or under control of an inducible or repressible gene component. Claim 5 is not further limiting of claim 1 be setting forth an agent that does not prevent dam DNA methyltransferase expression, by defining the agent to express dam DNA methyltransferase activity. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 7 recite a combination of claim limitations that are not internally consistent. Claim 5 and 7 depend from claim 1 that defines the agent to prevent expression of dam DNA methyltransferase activity, while claim 5 and 7 define the agent to express dam DNA methyltransferase activity. A construct that expresses dam DNA methyltransferase need not prevent Dam DNA methyltransferase activity as recited in claim 1. The invention is not clear or distinctly claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 1,3,5-7,9-10, 12-13,47-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Torreblanca et al(1996).

Torreblanca et al disclose a method of making a composition having reduced bacterial virulence of a pathogenic bacteria and the composition produced by said method, the method comprising the steps of:

Providing a virulent bacteria having a DNA methyltransferase activity (Salmonella typhimurium (see title); and

Contacting the bacteria with an agent that prevents the bacteria's dam gene expression by altering the bacteria's native level of methylation of adenine in a GATC tetranucleotide of the bacteria and thereby reducing virulence of the bacteria (see mutants (see page 20, col. 2, paragraphs 3-4), title, Table 1, page 17, insertional mutants and deletion mutants (see Table 1 and page 19, col. 2, paragraph 3). E.coli dam gene was inserted into the attenuated Salmonella host dam – strain through insertion of a plasmid that comprises the E.coli DNA adenine methyltransferase (dam) activity and over expressed (see page 20, col. 2, paragraphs 3-4).

The insertional mutation results from a nucleic acid sequence that bind to a native dam nucleic acid sequence of the bacteria and prevents the expression of the Dam gene due to the disruption of the coding sequence for dam activity (see Table 1, insertional mutant strains).

The reference anticipates the instantly claimed invention .

8. Claims 1,12-13,24,29-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Kleanthous et al (US Pat. 6,585,975, priority date April 30, 1998) as evidenced by Torreblanca et al (1996).

(Instant claims 1, 12 and 13) Kleanthous et al disclose method of making a composition having reduced bacterial virulence of a pathogenic bacteria and the composition produced by said method, the method comprising the steps of:

Providing a virulent bacteria having a DNA methyltransferase activity (Salmonella); and

Contacting the bacteria with an agent that prevents the bacteria's dam gene expression by altering the bacteria's native level of methylation of adenine in a GATC tetranucleotide of the bacteria and thereby reducing virulence of the bacteria (see mutants (An inactivated (see col. 2, lines 51-60; especially line 58 "genes") DNA Adenine Methylase Salmonella typhimurium attenuated (see col. 1, line 59-60, col. 3, lines 13-19; col. 3, lines 60-64) mutant (see col. 3, lines 6-7 and evidence provided by Torreblanca et al , 1996)).

(Instant claims 24, 29-31) The attenuated strain of Salmonella is used in a method of stimulating an immune response to a heterologous antigen for a pathogen, specifically the attenuated Salmonella so comprises a first heterologous nucleotide sequence, the heterologous nucleotide sequence being a coding sequence for an antigen of a microorganism that is a pathogenic

bacterium and causes gastric infection , specifically *Helicobacter pylori, H.felis, H. mustelae,* and *H.heilmanii* (see col. 1, lines 11-30, col. 4, lines 1-35), fused to a second heterologous nucleic acid encoding an antigen from an enteric pathogen (see col. 5, lines 46-67).wherein the altered DAM activity is inactivated, and the first heterologous nucleotide sequence is operatively inserted into a first plasmid (see col. 4, lines 3-10). The presence of a second mutations aids in preventing reversion of the strain to wild type, specifically a combination of dam together (col. 1, lines 58-67;see all claims) and the composition comprises a pharmaceutically acceptable carrier (see at least col. 6-7).

The reference inherently anticipates the instantly claimed invention.

9. Claims 1,5-7,9-10,12,14-15,47,49 are rejected under 35 U.S.C. 102(b) as being anticipated by Bandyopadhyay et al (1994).

Bandyopadhyay et al disclose a method of making a composition having reduced bacterial virulence of a pathogenic bacteria and the composition produced by said method, the method comprising the steps of:

Providing a virulent bacteria (Vibrio cholera or E.coli) having a DNA methyltransferase activity (see title); and

Contacting the bacteria (E.coli) with an agent that prevents the bacteria's dam gene expression by altering the bacteria's native level of methylation of adenine in a GATC tetranucleotide of the bacteria and thereby reducing virulence of the bacteria (see page 68, col. 2, last paragraph). Vibrio cholera dam gene was inserted into E.coli host dam – strain (see page 68, col. 1, paragraph 3, "GW3810") through insertion of a mutation, as well as complementation

with a plasmid that comprises the Vibrio cholera DNA adenine methyltransferase (dam) activity Additionally Vibrio cholera was transformed with the dam gene for over production of DNA adenine methyltransferase. (see page 69, col. 1 and 2 "overproduction").

The insertional mutation results from a nucleic acid sequence that bind to a native dam nucleic acid sequence of the bacteria and prevents the expression of the Dam gene due to the disruption of the coding sequence for dam activity (see Table 1, insertional mutant strains).

The composition comprises a diluent (a species of the instantly claimed excipients), specifically minimal media containing 1% casamino acids (see page 69, col. 2, Fig. 3 legend narrative) , a DNA Adenine Methylase E,.coli mutant (E.coli GW3810) that comprises a first heterologous nucleotide sequence, the heterologous nucleotide sequence being a coding sequence for an antigen of Vibrio cholera, a pathogen that causes an enteric infection. The Vibrio cholera antigen encoded by the heterogeneous nucleotide sequence is DNA Adenine Methylase antigen,wherein the altered DAM activity is through the presence of a second heterologous nucleotide sequence, (see page 68, col. 1, paragraph 3 "GW3810 (JM103 dam::Tn9) , and over expression of the first heterologous nucleotide sequence which evidences DAM activity, wherein the first heterologous nucleotide sequence is operatively inserted into a first plasmid (see Figure 1, page 68, plasmid encoding Vibrio cholera Dam methylase and col. 2, paragraph 1). The reference anticipates the instantly claimed invention directed to dam mutant strains that express a Vibrio cholera heterologous coding sequence of an antigen, specific Dam methyltransferase.

The reference anticipates the instantly claimed invention .

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims ,3,5-7, 28, 32-33 and 48-50 rejected under 35 U.S.C. 103(a) as being unpatentable over Kleanthous et al in view of Terreblanca et al.

See discussion of Kleanthous et al above. The reference teaches a attenuated strain of Salmonella with an inactivated dam gene and a method of inducing an immune response

in a mammal, to include humans, but differs from the instantly claimed invention by failing to show the inactivation of the dam gene by genetic means.

Terreblanca et al teach and show the production of recombinant Salmonella strains that evidence inactivated dam genes utilizing genetic means (see Table 1) in an analogous art for the purpose of producing double mutant attenuated strains of Salmonella typhimurium lacking or overproducing DNA adenine methylase activity (see abstract and page 20, col. 2, paragraphs 3-4).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to inactivate the Salmonella mutant of Kleanthous et al with the genetic means of Terreblanca et al because both Kleanthous et al and Terreblanca et al produce attenuated strains of Salmonella with inactivated dam genes, and Terreblanca et al disclose a plurality of genetic means that are combinable into double mutant strains of Salmonella (see Terreblanca et al, page 24, col. 1, paragraph 4) that are viable and stable mutants (see page 24, col. 1, paragraph 1).

In the absence of a showing of unexpected results, Kleanthous et al in view of Terreblanca et al obviates the instantly claimed invention as the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a dam mutant strains which has been altered with a genetic or DNA agent because Terreblanca et al teaches specific genotypes that evidence desired phenotypic characteristics of being viable (see abstract) and attenuated and could readily serve as a vaccine vector for induction of an immune response as taught by Kleanthous et al.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Arraj, JA et al is cited to show phenotypic reversal in dam mutants of E.coli (1983).

14. Bassing et al (1992) is cited to show a methyltransferase gene of Haemophilus influenzae.

15. Benkovic et al (US Pat. 6,413,751) is cited to show a recombinant host cell that comprises H.pylori DNA adenine methyltransferase (see claim 4) and said host cell would therefore inherently comprise an agent that alters DNA adenine methyltransferase activity.

16. Guha et al is cited to show E.coli dam gene in Bacillus subtilis (1992).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
November 8, 2004

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